

Appl. No. : 10/066,500
Filed : February 1, 2002

REMARKS

Claims 40-47, 50-52 and 56-72 are pending in the present application. Applicants respond below to the specific rejections raised by the Examiner in the final Office Action mailed July 21, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 102- Utility

The Examiner maintains the rejection of Claims 40-47, 50-52 and 56-72 as allegedly lacking a specific, substantial, and credible utility for the reasons set forth in the Office Actions mailed March 16, 2005, and October 28, 2004. The Examiner maintains that Applicants' asserted utilities for nucleic acids encoding PRO444, such as treatment of pericyte-associated tumors and stimulating angiogenesis, "are not supported by any factual evidence of record or sound scientific reasoning." The Examiner maintains that because many factors and signals can activate *c-fos*, and because the role of *c-fos* is not limited to cancer, there is "no scientific support for [the] conclusion that activation of *c-fos* in pericytes by PRO444 is specifically associated with carcinogenesis of pericytes." Office Action at 3. The Examiner also argues that the specification lacks evidence or reference to scientific literature that support a nexus between activation of *c-fos* in pericytes and angiogenesis. *Id.*; Office Action at 4.

The Examiner argues that the involvement of pericytes in angiogenesis is controversial and not fully understood, and cites to Diaz-Florez as support. *Id.* The Examiner therefore asserts that "in view of the lack of knowledge as to the biological significance of the polypeptide of SEQ ID NO:9 with respect to cancer or angiogenesis," further research would be required to identify or confirm a "real world use" for the claimed nucleic acids. *Id.*

The Examiner also argues that although *c-fos* is a known proto-oncogene and that the role of *c-fos* in cancer has been closely investigated, Coulon *et al.*, Herrera *et al.*, and Janknecht *et al.* demonstrate that *c-fos* is induced by growth factors, serum, UV light, seizures, and increased intracellular calcium. Therefore, the Examiner concludes that not every stimulus that results in activation of *c-fos* relates to its role in cancer. Office Action at 5. The Examiner maintains the position that there is no scientific support for the conclusion that activation of *c-fos* in pericytes by PRO444 is specifically associated with carcinogenesis of pericytes. Office Action at 4.

Applicants respectfully disagree.

Appl. No. : 10/066,500
Filed : February 1, 2002

Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that “Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” Further, “to violate § 101 the claimed device must be totally incapable of achieving a useful result.” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular

Appl. No. : 10/066,500
Filed : February 1, 2002

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that “to overcome the presumption of truth that an assertion of utility by the applicant enjoys” the PTO must establish that it is “more likely than not that one of ordinary skill in the art would doubt (i.e., ‘question’) the truth of the statement of utility.” M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

Appl. No. : 10/066,500
Filed : February 1, 2002

utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004)
(underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

Appl. No. : 10/066,500
Filed : February 1, 2002

[I]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful to treat tumors by affecting neovascularization and for the stimulation of angiogenesis.

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert they have provided reliable evidence that PRO444 stimulates *c-fos* in pericytes. As discussed below, at the time the application was filed, it was well known that pericytes are involved in angiogenesis. Specifically, studies had shown that pericytes are present in newly formed capillary sprouts, and that pericytes are involved in later stages of angiogenesis, including survival of newly formed vasculature, for example by secretion of VEGF. It was also well known at the time the application was filed that VEGF is a potent angiogenic factor, and the VEGF expression is regulated by *c-fos*. Thus, Applicants submit that based on the involvement of pericytes and VEGF in neovascularization and also their role in cancer, as well as the role of *c-fos* in regulation of VEGF expression, the skilled artisan, like Applicants, would more likely than not believe that PRO444, as a stimulator of *c-fos* in pericytes, is useful as a therapeutic target for pathological angiogenesis, as well as a tool for stimulating angiogenesis.

Applicants understand the Examiner to be making the following arguments in response to Applicants' asserted utilities:

1. The Examiner argues that there is no evidence that PRO444 *c-fos* induction in pericytes is specifically related to cancer or angiogenesis. Office Action at 4. Citing Diaz-Florez et al. and Ozerdem et al (cited in the Office Action mailed March 16, 2005), the Examiner argues that the role of pericytes in angiogenesis is not fully understood, and therefore induction of *c-fos* cannot be specifically associated with cancer or angiogenesis.

2. Citing Janknecht et al., Herrera et al., and Coulon et al., the Examiner argues that several stimuli are capable of inducing *c-fos* expression, and therefore PRO444-induced *c-fos* induction is not a biological activity that can be particularly attributed to PRO444.

Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Further, Applicants submit that *even if* the PTO met its initial burden, Applicants have provided rebuttal evidence establishing that more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility of nucleic acids encoding PRO444 for tumor therapy, and to stimulate angiogenesis, is true.

As discussed in detail below, contrary to the Examiner's assertion, the art at the time of filing demonstrated that pericytes are involved in angiogenesis, and that VEGF was important in angiogenesis. Specifically, the references cited below demonstrate that VEGF functions as a potent angiogenic factor, and is closely involved in tumorigenesis due to its mitogenic stimulation of endothelial cells (EC's), as well as functioning as a survival factor for newly formed vessels. The references at the time of filing also established that VEGF expression is regulated by *c-fos*.

Finally, Applicants submit that the evidence offered by the Examiner in support of the rejection of Applicants' asserted utilities demonstrates *c-fos* induction in pericytes is involved in angiogenesis, and illustrates the soundness of Applicants' asserted utilities.

Pericytes have an established role in angiogenesis

Applicants submit herewith references illustrating the state of the art regarding pericyte control of angiogenesis at the time the application was filed. Nehls et al. (1992) *Cell Tissue Res.*

Appl. No. : 10/066,500
Filed : February 1, 2002

270:469-474 describes pericyte involvement in capillary sprouting during angiogenesis *in situ*. The authors induced angiogenesis in mouse mesentery tissue and used immunofluorescence to identify pericytes. The authors found that pericytes were regularly positioned at and in front of the advancing tips of endothelial sprouts, and bridging gaps between the leading edges of endothelial sprouts. The authors concluded that pericytes are involved in capillary sprouting. Rhodin et al., (1989), *J. Submicrosc. Cytol. Pathol.* 21:1-34 also found that pericytes were regularly found in association with most capillary sprouts examined. Rhodin et al., at 12. The role of pericytes in angiogenesis is also described in Ozerdem et al., cited by the Examiner. Specifically, the Ozerdem et al. study confirmed previous studies showing that pericytes contribute to angiogenic sprout formation in neoplastic neovascularization. Due to their role in angiogenesis, Ozerdem et al. suggests that "pericytes represent a target for treatment to up-regulate or down-regulate vascularization," for example in cancer. Ozerdem et al., at 248.

As discussed in further detail below, VEGF is a well-known and well-characterized potent angiogenic factor, and its role in pathological angiogenesis was well-documented at the time of filing of the application. At the time of filing of the instant application, studies had shown that VEGF is involved in survival of endothelial cells in newly formed vessels. Alon et al., (1995), *Nat. Med.* 1(10):1024-1028, examined the role of VEGF in retinopathy of prematurity (ROP), a disorder that ultimately results in blindness. It was generally accepted at the time that VEGF caused the abnormal vasoproliferation in ROP. Alon et al. showed that the absence of VEGF during the early stage in ROP resulted in blood vessel regression. Exogenously added VEGF reversed this process. Thus, Alon et al. concluded that VEGF is involved in survival of newly formed vasculature. The studies of Benjamin et al. (1997), *Proc. Nat. Acad. USA* 94:8761-8766, demonstrated this same phenomenon. Briefly, Benjamin et al. showed that shutting off VEGF expression in tumors resulted in regression of preformed tumor vessels. Notably, Benjamin et al. commented that this finding was "critical in the success of many angiogenic and anti-angiogenic therapies." Benjamin et al., at 8675. See also Fidler et al., (2000), *Cancer J.* 6(Suppl. 3) S225-236, for a discussion of the role of VEGF in survival of newly formed vasculature.

A review by Ellis et al. describes the role of pericytes in angiogenesis as it relates to tumor biology. Ellis, (2002), *Oncology* 16(5):14-22. Ellis explains that "the tumor

Appl. No. : 10/066,500
Filed : February 1, 2002

microenvironment is a caustic one. . .[t]herefore, for these fragile endothelial cells [that represent the new primitive capillary network] to survive, they must be exposed to endothelial cell survival factors. . .Endothelial cell survival factors include pericytes that may stabilize endothelium. . .by secretion of endothelial cell survival factors such as VEGF." Ellis, at 20. Thus, it was known that one of the roles in angiogenesis that pericytes play is to promote survival of newly formed vasculature, by secreting VEGF.

The Examiner maintains that both Diaz-Florez et al. and Otani et al. demonstrate that the involvement of pericytes in angiogenesis is not fully understood. Applicants disagree, and respectfully submit that both references support Applicants' position that pericytes have a known role in angiogenesis. Diaz Florez et al. is a review article summarizing the understanding of angiogenesis in 1994. The summary of the abstract lists the following "events" in neovascularization:

a) endothelial cell (EC) *and pericyte activation*; b) basal lamina degradation; c) *migration and proliferation of EC and pericytes*; d) formation of a new capillary vessel lumen; e) *appearance of pericytes around the new capillaries*; f) development of a new basal lamina; g) capillary loop formation; h) persistence or involution, and differentiation of the new vessels; and i) capillary network formation and, eventually, organization into larger microvessels. (emphasis added)

Although Diaz-Florez *et al.* states that angiogenesis is "complex," and that "*stepwise*, the current model of angiogenesis is controversial," Diaz-Florez *et al.* underscores Applicants' assertion that at the time the instant application was filed, pericytes were known to be essential in the process of angiogenesis. The passage of Diaz-Florez et al. cited by the Examiner states that "*most of the authors* are of the opinion that the involvement of capillaries with pericytes occurs at the end of the proliferative stage," (*Id.* at 818) which Applicants submit is addressed in the studies referenced above demonstrating the role of pericytes and VEGF in survival of newly formed vasculature. The same passage of Diaz-Florez elaborates on the "controversy" -- and explains that in contrast to the studies that the involvement of pericytes at the end of the proliferative stage of neovascularization, studies had also demonstrated "an early recruitment of pericytes during angiogenesis." *Id.* Diaz-Florez refers to studies showing "the fusion of pericytes with the endothelium at the point of active angiogenesis. . .and the presence of cytoplasmic processes of pericytes and EC caving in on each other. . .in the early stages of neovascularization. . .[and] nascent pericytes showing cellular processes advancing at the tips of

Appl. No. : 10/066,500
Filed : February 1, 2002

endothelial sprouts. . . suggesting that pericytes may serve as guiding structures of EC outgrowth." *Id.* Applicants submit that this is not a true "controversy" and as described below, merely reflects the fact that pericytes are involved in multiple stages of angiogenesis. The state of the art at the time the instant application was filed is summarized in Balabanov et al., (1998) *J. Neurosci. Res.* 53:637-644. Balabanov et al. state that "[p]ericytes have been implicated in all three stages of new vessel formation: 1) initiation, 2) sprout extension and migration, 3) maturation and cessation of growth," and notably mention that these functions "are thought to be mediated through. . . vascular endothelial growth factor." *Id.* at 640. Thus, the involvement of pericytes in neovascularization was well-established and recognized by those skilled in the art well before the filing of the instant application, and was not truly "controversial," as the Examiner asserts.

The involvement of pericytes in angiogenesis is further discussed in the studies of Ozerdem *et al.*, also cited by the Examiner for the proposition that the involvement of pericytes in angiogenesis was not fully understood. Ozerdem et al. found "the occurrence of pericyte tubes in early carcinoma tumors," noting the presence of "entire vessels [that] appear to be composed of pericyte tubes," and "large numbers of individual pericytes invading the tumors." Ozerdem *et al.* at 243. Ozerdem *et al.* also found "the pericytes and endothelial cells are both present at the growing tip of the vascular sprout." *Id.* The authors conclude that "activated. . . pericytes play an early role in the development of angiogenic sprouts and vessels," and underscore the early participation of pericytes in both physiological and pathological angiogenesis. *Id.* Notably, the authors conclude that pericytes represent an additional target for treatments designed either to up-regulate (for example in ischemic disorders), or down-regulate (for example in cancer) vascularization. *Id.* at 248.

The references cited above provide evidentiary support from the scientific literature of Dr. Gerritsen's testimony that at the time of filing of the instant application, it was known that "pericytes play an in important role in regulating angiogenesis" and that "pericytes help. . . stabilize newly formed blood vessels" (Gerritsen Decl., ¶6). The Examiner has offered no reason to doubt or any evidence to contradict Dr. Gerritsen's testimony.

VEGF has an established role in angiogenesis

Applicants submit that at the time the Application was filed, VEGF was widely-recognized as an angiogenic factor, playing a central role in pathogenic angiogenesis. Applicants submit herewith and discuss below references that demonstrate the state of the art at the time the application was filed regarding VEGF biology.

VEGF is a potent mitogen and a chemoattractant for endothelial cells (EC's). In addition VEGF promotes vascular permeability for EC's. Ferrara, N., (1995), *Breast Cancer Res.* 36:127-137, 127. Early studies demonstrated that VEGF promotes angiogenesis *in vitro*, by inducing confluent microvascular endothelial cells to invade a collagen gel and form tube-like structures. See, e.g., Pepper, M., et al. (1992), *Biochem. Biophys. Res. Comm.* 189:824-831. Augmented VEGF expression was known to be correlated with vascularization associated with increased tumor growth. (See, Benjamin et al., at 8671, and references cited therein). Inhibition of VEGF production or function was also shown to lead to inhibition of tumor growth. *Id.*, and references cited therein. This activity, in combination with VEGF's known function in mediating endothelial cell survival in newly formed vasculature, discussed above, led to the characterization of VEGF as "the pivotal *in vivo* mediator of. . .pathophysiological angiogenesis." Kolch et al., (1995) *Breast Cancer Res. Treat.* 36:139-155, at 139.

Applicants submit that the references cited above demonstrate that at the time the Application was filed, those skilled in the art appreciated the critical role of VEGF in angiogenesis, as required for neovascularization, survival of newly formed vasculature, and vascular permeability.

c-fos stimulates VEGF expression

As described in Janknecht, cited by the Examiner, *c-fos* encodes a subunit of the nuclear transcription factor AP-1. At the time the application was filed, *c-fos* was a widely-recognized proto-oncogene known to regulate cellular proliferation and differentiation. Janknecht at 443. At the time of filing of the instant application it was accepted by those skilled in the art that AP-1 played an important role in the expression of VEGF.

In 1990, Tishcer et al. analyzed the human gene for VEGF. Tischer et al. (1991), *J. Biol. Chem.* 266(18):11947-11954. The authors found that the promoter region for hVEGF contains several AP-1 binding sites, suggesting that *c-fos* is a regulator of VEGF expression. Tischer at

Appl. No. : 10/066,500
Filed : February 1, 2002

11953. Similarly, the structure of the mouse VEGF gene revealed "multiple consensus binding sties for AP-1." Shima, et al., (1996) *J. Biol. Chem.* 271(7):3877-3882, 3882. Further, in Kolch's review "Regulation of the expression of the VEGF/VPS and its receptors: role in tumor angiogenesis," ((1995) *Breast Cancer Res. Treat.* 36:139-155), Kolch summarizes the state of the art at the time by noting "[a]t present, a comprehensive assessment of several studies highlights the AP-1 transcription factor as an important common denominator for the regulation of VEGF expression." Kolch, at 144. Kolch highlights various pathways in which both *c-fos* and VEGF expression are regulated, including through the Ras and Raf pathways. *Id.* at 144-145. Kolch also links the induction of *c-fos* expression through the Raf and Ras pathways with conversion to a tumorigenic phenotype through activation of VEGF. *Id.* at 145.

Applicants submit that the references discussed above demonstrate that at the time the instant application was filed, those skilled in the art appreciated the role of *c-fos* in VEGF expression, and hence, the role of *c-fos* in the angiogenic process, including neovascularization and stabilization of newly formed vasculature.

The skilled artisan would believe that indirect regulators of angiogenic factors (VEGF) are useful as therapeutic targets for cancer therapy

As Dr. Gerritsen testified, Applicants submit that "a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes (*e.g.*, PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis." Gerritsen Decl., ¶6. The discussion above demonstrates that at the time of filing of the instant application, those skilled in the art appreciated the role of pericytes in capillary sprout formation and the survival of neovasculature. Further, the art at the time demonstrated that VEGF was expressed in pericytes, and that VEGF is involved in both proliferation of EC cells and in survival of newly formed vasculature. Finally, those skilled in the art appreciated the central role of *c-fos* in VEGF expression. Thus, Applicants submit, and as Dr. Gerritsen testified, a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes would be useful in tumor therapy.

As proof of this principle, in a review entitled "Angiogenesis Inhibitors in Oncology," Ellis states that anti-angiogenic strategies involved, among others, strategies that decrease the activity of specific angiogenic factors (such as VEGF), and strategies that indirectly

downregulate activity of angiogenic and survival factors. Ellis et al., (2002) *Oncology* 16(5):14-22. Ellis proposes that "[s]trategies that downregulate the upstream signaling pathways to VEGF and other angiogenic factors may indirectly downregulate VEGF activity and angiogenesis." Ellis, at 20. Applicants submit that Ellis' discussion of various strategies for cancer therapy describes identification of compounds such as PRO444, that act indirectly to regulate the activity of angiogenic and survival factors, such as VEGF, demonstrating that those skilled in the art believe that compounds such as PRO444 are useful in cancer therapy.

Applicants note that the first strategy proposed by Ellis has been demonstrated to be effective. A VEGF-specific antibody, bevacizumab, has been successfully used to treat several cancer types. See, Kirkpatrick, P., (2005), *Nat. Rev. Drug Disc.* S8-S9. Willett et al. report that bevacizumab has antivasculature effects in human rectal cancer. Willett et al. (2004) *Nature Medicine*, 10(2):145-147.

In summary, Ellis' discussion provides support for Dr. Gerristen's testimony that those skilled in the art would more likely than not believe that factors that induce the expression of *c-fos*, a known upstream regulator of VEGF, are useful targets for tumor therapy.

c-fos activation in pericytes has a specific activity associated with angiogenesis

Applicants next address the Examiner's arguments that Coulon et al., Herrera et al., and Janknecht et al. demonstrate that there can be no specific function attributable to PRO444 induction of *c-fos* in pericytes since many factors are known to stimulate *c-fos*. As an initial matter, Applicants submit that none of the above references discusses *c-fos* activation in pericytes, and are thus not relevant to Applicants' asserted utility. Coulon et al. is a study of *c-fos* activation in mouse fibroblasts. Herrera et al. is a study of *c-fos* activation in brain cells. Accordingly, the teachings of these references are not necessarily applicable to pericytes, the specific cell type tested in Assay 93, or angiogenesis. Janknecht et al. is a generic commentary on *c-fos* activation entitled "Signal integration at the *c-fos* promoter," that provides an overview of various factors that have been shown to stimulate *c-fos*. Janknecht et al. does not provide discussion or teachings relating to *c-fos* stimulation in any particular cell type, including pericytes. By contrast, Sakurai et al. and Otani et al. are the only two references cited by the Examiner that address *c-fos* activation in pericyte cells. Janknecht et al., Sakurai et al. and Otani et al. are discussed below.

Appl. No. : 10/066,500
Filed : February 1, 2002

The Examiner has correctly pointed out that Janknecht et al. teaches that *c-fos* can be induced by growth factors, serum, and mitogenic signals such as UV light. However, as is the case with Coulon et al. and Herrera et al., Janknecht et al. is completely silent regarding *c-fos* expression in pericytes. Applicants do note that Janknecht et al. teaches that Platelet Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), IL-6 and IL-2 stimulate *c-fos*. It is not surprising that of these four compounds discussed by Janknecht et al., PDGF, EGF and IL-6 are well-known angiogenic factors. See, Zoltan et al. (1999), *Trends in Glycosci. and Glycotech.* 11:73-93, 75; Fidler et al. at S225; Ellis et al. at 16. As taught in McColl et al. (2004), APMIS 112:463-480, 467, "since *fos* is upregulated by [various stimuli including growth factors], VEGF expression could also be elevated in response to these stimuli, *as is indeed the case.*" (emphasis added) Thus, Applicants submit that while various factors may stimulate *c-fos*, several of these very factors are also involved in angiogenesis, tying the role of *c-fos* activation to angiogenesis.

As correctly stated by the Examiner in the previous Office Action, Sakurai et al. and Otani et al., show that *c-fos* activation in pericytes can be achieved through prostaglandins and angiotensin II, respectively. The Examiner argued that these findings demonstrate that no function can be attributed to PRO444 with respect to its ability to activate *c-fos* in pericytes, because "many growth factors are capable to stimulate growth of pericytes through activation of [the] *c-fos* pathway." Office Action mailed March 16, 2005, at 5.

Applicants submit that activation of *c-fos* in pericytes by prostaglandins, angiotensin II, and VEGF all lead to angiogenesis, and have all been implicated in pathological angiogenesis. Sakurai et al., cited by the Examiner, examined the role of prostaglandins in proliferative retinopathy, in which "the underlying mechanism. . . is the formation of new vessels." Sakurai et al., at 2774. The authors hypothesized that prostaglandins, well-known inflammatory mediators, may play a role in the development of new vessels. *Id.* Pericytes treated with prostaglandins induced *c-fos* expression, and as anticipated, also showed increased levels of VEGF expression, "a key growth factor in neovascularization." *Id.* The authors conclude that their findings provide an explanation "for the known link between angiogenesis and chronic inflammation," *Id.* at 2780. Thus, contrary to the Examiner's position, Sakurai et al. demonstrates that factors that stimulate *c-fos* in pericytes lead to stimulation of VEGF, and angiogenesis.

Appl. No. : 10/066,500
Filed : February 1, 2002

The second reference that the Examiner cites which relates to *c-fos* activation in pericytes is Otani et al. Otani et al. observed that angiotensin II and VEGF activate *c-fos* in pericytes. These data are fully consistent with Applicants' assertion that *c-fos* activation in pericytes, *e.g.*, by PRO444, angiotensin II, or VEGF, leads to a specific biological activity -- angiogenesis. Otani et al. examined the role of angiotensin II in retinal pericytes. The authors found the angiotensin II induced VEGF expression in bovine pericytes, through the *c-fos* pathway. The authors also found that VEGF released by the pericytes stimulated retinal endothelial growth, and summarized their findings by stating that "[t]hese findings suggest that AII might induce angiogenic activity through a paracrine function of VEGF in retinal microvascular cells." Otani et al., at 1192. Thus, the authors found that *c-fos* indirectly induced angiogenesis through VEGF.

As shown above, the references relied upon the Examiner as supporting the position that no specific activity can be attributed to PRO444, since other factors are known to stimulate *c-fos* in pericytes, either are not relevant to the issue of whether *c-fos* activation in pericytes is associated with angiogenesis, or alternatively fully support Applicants' position. In the only two references cited by the Examiner which examine *c-fos* activation in pericytes, the authors discovered that *c-fos* induction led to VEGF induction, which led to angiogenesis. Therefore, the references cited by the Examiner demonstrate that those skilled in the art would more likely than not believe that PRO444, as an inducer of *c-fos* in pericytes, would promote angiogenesis, and as such is a useful therapeutic target for pathological angiogenesis.

Conclusion

Applicants submit that the evidence submitted herewith establishes that factors capable of inducing *c-fos* in pericyte cells are useful tools for stimulating angiogenesis and as useful tools to design anti-angiogenic therapeutics, for example for tumor therapy. First, Applicants demonstrated that at the time the application was filed, the role of pericytes in angiogenesis -- specifically capillary sprout formation and survival of neovasculature - had been established. Applicants also presented evidence that the role of VEGF as a potent angiogenic factor and as a survival factor for newly formed vasculature was established. Further, Applicants also presented evidence that it was known that *c-fos* played a central role in VEGF expression. Taken together, the above evidence establishes that more likely than not, one skilled in the art would have believed Applicants' asserted utilities for nucleic acids encoding PRO444 at the time of filing of

Appl. No. : 10/066,500
Filed : February 1, 2002

the application. As proof of this, Applicants provided evidence that those skilled in the art had postulated that upstream regulators of VEGF are useful targets for tumor therapy, demonstrating that those skilled in the art would believe PRO444, as an upstream regulator of VEGF in pericytes, is useful for angiogenic and anti-angiogenic therapies, such as tumor therapy. Finally, Applicants have shown that the evidence presented by the Examiner regarding *c-fos* activation in pericytes, rather than establishing that PRO444 lacks specific and substantial utility, clearly demonstrates that those skilled in the art accept the theory upon which Applicants' asserted utility rests, *i.e.*, that stimulation of *c-fos* in pericyte cells leads to angiogenesis.

Applicants submit that it is more likely than not that one skilled in the art would believe Applicants' asserted utility for nucleic acids encoding PRO444. Applicants respectfully request that the Examiner withdraw the rejection of Claims 40-47, 50-52 and 56-72 under 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

The Examiner has maintained the rejection of Claims 40-47, 50-52 and 56-72 as not being enabled since the claimed invention is allegedly not supported by either a specific and substantial asserted utility, or a well-established utility.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has rejected Claims 40-44 and 56-59 as allegedly containing subject matter which was not adequately described in the specification. In particular, the Examiner states that "one can *easily envision* the genus of nucleic acid molecules" which are at least 80 percent identical to SEQ ID NO:9, however, the Examiner maintains that the specification does not describe those nucleic acids within the genus that are capable of inducing *c-fos* in pericytes. Office Action at 9. According to the Examiner, there is not information regarding conserved structural features for all the molecules within the genus, "or a representative number of species, *method of production*, or any other characteristic that would allow a skilled artisan to immediately understand what is claimed." *Id.* Further, the Examiner asserts that because various

Appl. No. : 10/066,500
Filed : February 1, 2002

stimuli can induce *c-fos*, the skilled artisan could not distinguish variants of SEQ ID NO:8 that have the ability to induce *c-fos* from variants of SEQ ID NO:8 that do not have this function.

Applicants respectfully disagree.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure “reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter.” *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant’s disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the rejected claims concerns nucleic acids encoding a polypeptide having 80% to 99% sequence identity to SEQ ID NO:9, with the functional recitation “wherein said isolated nucleic acid encodes a polypeptide having the ability to induce *c-fos* expression.” Applicants submit that the specification and the rejected claims are indistinguishably analogous

Appl. No. : 10/066,500
Filed : February 1, 2002

to the description and claims presented in Example 14 of the written description training materials. Example 14 provides:

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of $A \rightarrow B$. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim: A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of $A \rightarrow B$.

In the Example, a single species was disclosed, and there was actual reduction to practice of only the single, disclosed species, *i.e.*, SEQ ID NO:3. Nevertheless, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to SEQ ID NO:3. The Guidelines explain that the claimed variants do not have substantial variation since "all of the variants must possess the specified catalytic activity and must have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Just as the specification in the guidelines discloses a protein isolated from liver that catalyzes the reaction of $A \rightarrow B$, the instant specification describes the isolation and characterization of a nucleic acid sequence encoding a protein that induces *c-fos* activity in pericyte cells. *See*, Example 60, Assay 93. Further, similar to the specification in the guidelines, the instant specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. *See*, "PRO Polypeptide Variants," p. 71, line 29- p. 72, line 28. The instant specification, like Example 14, indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art. *Id.* As is the case with the specification in Example 14, Example 60 of the instant specification provides an assay for detecting the catalytic activity of SEQ ID NO:9 and variants thereof. Finally, as is the case with the claim in Example 14, the claims rejected in the instant application also have very high sequence homology - *i.e.*, at least 95% - to the disclosed sequences. Thus, Applicants' disclosure and claims are indistinguishable

Appl. No. : 10/066,500
Filed : February 1, 2002

from those discussed in Example 14 of the written description guidelines, which according to the PTO, meets the requirements of 35 U.S.C. § 112, first paragraph.

Finally, Applicants note that the instant case is not only identical to Example 14 of the Written Description Guidelines as discussed above, but it is also similar to a recent Federal Circuit Court of Appeals decision as well. In *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

[W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.

Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the applicants in *Wallach* to actually make or individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that only a single sequence was disclosed, and the encompassed genus was enormous due to codon degeneracy in the genetic code. The Court reasoned that because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to place the applicants in possession of the enormous genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NOs:8 and 9, and claim nucleic acids which are at least 80% identical to them or nucleic acids which encode them, and which meet the functional limitation of encoding a polypeptide

Appl. No. : 10/066,500
Filed : February 1, 2002

that stimulates *c-fos* in pericytes. As discussed above, it is routine in the art to create nucleic acids which have at least 80% - 99% sequence identity to the recited sequence related to SEQ ID NOs:8 and 9 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, how to determine which encoded polypeptides stimulate *c-fos* expression is well within the knowledge of those skilled in the art, particularly in light of the assay disclosed in Example 60 of the instant specification. The predictability of this structure/function combination is sufficient to place the claimed subject matter in the possession of the Appellants, and thus the claimed polypeptides are adequately described. Like Example 14 of the Written Description Guidelines, the *Wallach* opinion makes clear that there is no need to literally describe more than a single species to adequately describe a large genus where one of skill in the art recognizes that the disclosed species puts the applicant in possession of the claimed genus.

Applicants note that the limitation “wherein said isolated nucleic acid encodes a polypeptide having the ability to induce *c-fos* expression” was not added to Claim 45 because Claim 45 does not claim variants of SEQ ID NOs:8 or 9. As in *Wallach*, Applicants have disclosed a single polypeptide sequence, and therefore they are in possession of every nucleic acid which encodes the disclosed sequence. In light of *Wallach*, any rejection of Claims 40-44 and 56-59 for lack of written description is clearly erroneous.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:8 and SEQ ID NO:9 and by describing the *c-fos* induction assay, which results in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to “recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.” Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Appl. No. : 10/066,500
Filed : February 1, 2002

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 18, 2005

By: AnneMarie Kaiser

AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

1936428
091505